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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,658	12/11/2001	Susan C. Bock	21101.0004U3	7477

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,658	BOCK ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12-11-01 AND 9-29-03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Preliminary Amendments filed 12/11/01 and 10/11/02 have been entered. Claims 1-15 (as indicated in the Amendment filed 10/11/02) and Claims 16-49 (as indicated in the Amendment filed 12/11/01) have been cancelled and Claims 50-142 have been added. Therefore, Claims 50-142 are presently pending and have been considered in this Office Action.

Information Disclosure Statement

The papers filed with the Information Disclosure Statement filed 12/11/01 include a Notice of References Cited from the parent Application (09/305,588) that includes the Cunningham et al. reference. To prevent confusion and to ensure that the Cunningham et al. reference is properly cited in the prosecution of the present case, the examiner has included a Notice of References Cited attached hereto which cites Cunningham et al. The reference has been considered.

Claim Objections

Claim 112 is objected to due to the following informalities: Claim 112 has two periods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65, 66, and 98-142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 65 and 66 are indefinite as to which sequence is being claimed. Both claims are directed to an elastase-resistant antithrombin III comprising an amino acid sequence at residues 387-391 of SEQ ID NO:35. However, both claims are unclear as to how the corresponding residues of SEQ ID NO:4 having the sequences shown at residues 3 through 7 of SEQ ID NO:4 (claim 65) or SEQ ID NO:5 (claim 66) relate to the claimed sequence. Clarification is required.

Claims 98, 101, 104, 108, 112-115, 121, 124, 127, 131, and 134-138 contain the phrase "at least about" which is indefinite because "at least" implies a definite lower limit of the recited activity whereas "about" is a term that is flexible and implies that the range claimed might be somewhat below the lower limit. Moreover, the Specification and prior art do not provide any guidance as to the range of activity covered by "about". Claims 99-100, 102-103, 105-107, 109-111, 116-120, 122-123, 125-126, 128-130, 132-133, and 139-142 are also rejected since they depend from the rejected base claims yet do not correct the deficiencies noted above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-143 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antithrombin III with increased resistance to human neutrophil elastase comprising modifications at the amino acid positions specifically defined in the claims wherein the ATIII has a half life of inactivation by human neutrophil elastase of at least 2.1 minutes and retains a thrombin or factor Xa inhibitory activity defined by a k_{app} of $0.2M^{-1}sec^{-1} \times 10^3$ or a thrombin inhibitory activity of from about 2% to about 73% of plasma ATIII thrombin inhibitory activity or a factor Xa inhibitory activity of at least 12.5% of plasma ATIII factor Xa inhibitory activity, does not reasonably provide enablement for an elastase-resistant antithrombin III comprising modifications at the amino acid positions specifically defined in the claims wherein the ATIII retains a thrombin or factor Xa inhibitory activity defined by a k_{app} of $0.2M^{-1}sec^{-1} \times 10^3$ or a thrombin inhibitory activity of at least 2% of plasma ATIII thrombin inhibitory activity or a factor Xa inhibitory activity of at least 12.5% of plasma ATIII factor Xa inhibitory activity . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount

of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Nature of the Invention:

The invention is directed to solving the problem of the very large doses of antithrombin III (ATIII) required in the treatment of septic DIC due to ATIII inactivation by elastase which is elevated during septic DIC. The invention is drawn to ATIII having substitutions at specific amino acid positions close to the site of elastase cleavage in order to inhibit cleavage by elastase.

Breadth of the claims:

Elastase-Resistant—The claims are so broad as to include ATIII proteins that are completely resistant to elastase cleavage.

Thrombin Inhibition Activities greater than plasma ATIII—The claims are so broad as to encompass ATIII proteins that have thrombin inhibitory activity greater than unmodified plasma ATIII. The examiner notes that, the phrase "retains...activity defined by a k_{app} of $0.2M^{-1}sec^{-1}$ $x10^{3}$" in Claims 50-97 is interpreted to mean that the claimed ATIII has at least the claimed rate of activity.

Amount of direction or guidance presented/Presence or absence of working examples:

The specification provides examples of the activities of ATIII mutants containing substitutions at various positions (see Table 3, page 57 of present Specification). The mutants have half-lives of inactivation by human neutrophil elastase from about 2.1 to

about 437 minutes. The mutant that had the half-life of 437 minutes had very minimal thrombin and factor Xa inhibitory activity. None of the mutants were completely resistant to elastase and none of the mutants had a thrombin inhibitory activity greater than unmodified plasma ATIII (4.9 x103 M-1s-1; see Table 3).

State of the prior art/relative skill of those of the prior art:

A search of the prior art did not reveal any ATIII proteins having the claimed amino acid substitutions at the claimed amino acid positions or ATIII proteins that are resistant to elastase inactivation. Cunningham et al. (Thrombosis Res. (1997) 88(2): 171-181; cited in IDS) teaches that the elastase cleavage sites of ATIII were well known at the time of the invention and indicate that ATIII inactivation has been proposed to contribute to thrombotic events arising in inflammatory states (p. 172, 2nd paragraph). Cunningham et al. examine the effect of making substitutions at the elastase cleavage sites (P4 and P5) in an attempt to make an elastase resistant ATIII. Cunningham et al. show that a P4Ser mutation results in an inactive ATIII and that P4Trp or P4/P5 Trp/Trp variants retain sensitivity to elastase inactivation (see Discussion). Cunningham et al. teach that LE may cleave at secondary sites if its primary cleavage sites are blocked (see Discussion).

Predictability/Unpredictability of the Art

The effect an amino acid substitution has on a particular protein activity is highly unpredictable. As suggested in Cunningham et al., it is unpredictable as to whether elastase cleaves at a secondary site when its primary site is blocked by mutagenesis (see Cunningham et al. page 179, paragraph 4). In addition, the region that is mutated

in the present invention is involved in several different activities including elastase mediated inactivation, linking the hinge region with the reactive center, and activating conformation change to the reactive center when ATIII binds heparin (see Cunningham et al. p. 178). Thus, the effect of a mutation is complicated by the many functions it may affect. Moreover, comparing the results of Cunningham et al. to the present invention further illustrate the unpredictability of mutation to obtain increased ATIII resistance to elastase inactivation. Cunningham et al. was unsuccessful in obtaining increased ATIII resistance to leukocyte elastase by making mutations at the P4 and P5 resistance whereas the present invention shows that substitution of different amino acids at the same positions as in Cunningham et al. results in increased neutrophil elastase resistance.

Quantity of Experimentation:

Therefore, the quantity of experimentation required to make an ATIII that is completely resistant to elastase and that has a useful activity level (keeping in mind that the purpose of making such a mutant is to lower the dosages of ATIII required in treatments or increase the potency of ATIII) is undue because it would not merely require repetition of what Applicant has done but would require a substantial inventive contribution to find an ATIII mutant that was completely resistant to neutrophil elastase and/or had thrombin inhibitory or factor Xa inhibitory activity greater than unmodified plasma ATIII. Thus, for the reasons discussed above, the full scope of the claims do not appear to be supported by an enabling disclosure.

Conclusions

No Claims are allowable. The claimed ATIII mutants having the activities (including elastase resistance) discussed in the rejections above are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
April 2, 2004

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